**Revamping Oral Drug Absorption Pharmacokinetics with Scientific and Regulatory Implications**

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**Supplementary Information**

**Appendix**

In the ensuing equations we use a number of symbols that we define as follows:

*t*: time

*C*: drug concentration in the blood

*C*P: drug concentration in the peripheral compartment in a two-compartment model

*F*: fraction of administered dose absorbed

*D*: dose

*V*d: volume of distribution

*V*c: volume of central compartment in a two-compartment model

*k*a: absorption rate constant

*k*el: elimination rate constant

*k*10: elimination rate constant from central compartment

*k*12: central-to-peripheral compartment rate constant

*k*21: peripheral-to-central compartment rate constant

*AUC*: area under the concentration, time curve

*A*: amount of drug absorbed

*τ*, *τ*1, *τ*2: finite time for absorption or for stage 1 or for stage 2

Model equations and derived forms for *AUC* and *A*.

**Classical models**

Classical *one-compartment model* with infinite time, first-order absorption and elimination.

$C\left(t\right)=\frac{FDk\_{a}}{V\_{d}\left(k\_{a}-k\_{el}\right)}\left(e^{-k\_{el}t}-e^{-k\_{a}t}\right)$ (Α1)

$\left[AUC\right]\_{0}^{t}=\frac{FDk\_{a}}{V\_{d}\left(k\_{a}-k\_{el}\right)}\left(\frac{1-e^{-k\_{el}t}}{k\_{el}}-\frac{1-e^{-k\_{a}t}}{k\_{a}}\right)$ (Α2)

$\left[AUC\right]\_{0}^{\infty }=\frac{FD}{V\_{d}k\_{el}}$ (Α3)

$\frac{A\left(t\right)}{A\left(\infty \right)}=1-e^{-k\_{a}t}$ (Α4)

Classical two-compartment model with infinite time, first-order absorption and disposition.

We define

$b=k\_{12}+k\_{21}+k\_{10}$, $c=k\_{21}k\_{10}$, $d=b^{2}-4c$, $α=\frac{b+\sqrt{d}}{2}$, $β=\frac{b-\sqrt{d}}{2}$ (Α5)

Hence $αβ=k\_{21}k\_{10}$, $α+β=k\_{12}+k\_{21}+k\_{10}$ (A5a)

$B\_{1}=\frac{FDk\_{a}\left(k\_{21}-α\right)}{V\_{c}\left(β-α\right)\left(k\_{α}-α\right)}$ (Α6)

$B\_{2}=\frac{FDk\_{a}\left(k\_{21}-β\right)}{V\_{c}\left(α-β\right)\left(k\_{α}-β\right)}$ (Α7)

$B\_{3}=\frac{FDk\_{a}\left(k\_{21}-k\_{α}\right)}{V\_{c}\left(β-k\_{α}\right)\left(α-k\_{α}\right)}$ (Α8)

$C\left(t\right)=B\_{1}e^{-αt}+B\_{2}e^{-βt}+B\_{3}e^{-k\_{α}t}$ (Α9)

$\left[AUC\right]\_{0}^{t}=B\_{1}\frac{1-e^{-αt}}{α}+B\_{2}\frac{1-e^{-βt}}{β}+B\_{3}\frac{1-e^{-k\_{α}t}}{k\_{α}}$ (Α10)

$\left[AUC\right]\_{0}^{\infty }=\frac{B\_{1}}{α}+\frac{B\_{2}}{β}+\frac{B\_{3}}{k\_{α}}$ (Α11)

$\frac{A\left(t\right)}{A\left(\infty \right)}=\frac{\frac{B\_{1}}{α}\left(k\_{10}+\left(α-k\_{10}\right)e^{-αt}\right)+\frac{B\_{2}}{β}\left(k\_{10}+\left(β-k\_{10}\right)e^{-βt}\right)+\frac{B\_{3}}{k\_{α}}\left(k\_{10}+\left(k\_{α}-k\_{10}\right)e^{-k\_{α}t}\right)}{k\_{10}\left(\frac{B\_{1}}{α}+\frac{B\_{2}}{β}+\frac{B\_{3}}{k\_{α}}\right)}$ (Α12)

**PBFTPK models**

*One-compartment model* with zero-order, finite time absorption of duration *τ*.

For $0<t\leq τ$,

$C\left(t\right)=\frac{FD}{τV\_{d}k\_{el}}\left(1-e^{-k\_{el}t}\right)$ (Α13)

$\left[AUC\right]\_{0}^{t}=\frac{FD}{τV\_{d}k\_{el}}\left[t+\frac{e^{-k\_{el}t}-1}{k\_{el}}\right]$ (Α14)

$C\left(τ\right)=\frac{FD}{τV\_{d}k\_{el}}\left(1-e^{-k\_{el}τ}\right)$ (Α15)

$\left[AUC\right]\_{0}^{τ}=\frac{FD}{τV\_{d}k\_{el}}\left[τ+\frac{e^{-k\_{el}τ}-1}{k\_{el}}\right]$ (Α16)

$C\left(t\right)+k\_{el}\left[AUC\right]\_{0}^{t}=\frac{FD}{τV\_{d}}t$ (Α17)

$\frac{A\left(t\right)}{A\left(τ\right)}=\frac{C\left(t\right)+k\_{el}\left[AUC\right]\_{0}^{t}}{C\left(τ\right)+k\_{el}\left[AUC\right]\_{0}^{τ}}=\frac{t}{τ}$ (Α18)

For $τ<t$,

$C\left(t\right)=C\left(τ\right)e^{-k\_{el}\left(t-τ\right)}$ (Α19)

$\left[AUC\right]\_{0}^{t}=\left[AUC\right]\_{0}^{τ}+C\left(τ\right)\frac{1-e^{-k\_{el}\left(t-τ\right)}}{k\_{el}}$ (Α20)

$C\left(t\right)+k\_{el}\left[AUC\right]\_{0}^{t}=C\left(τ\right)+k\_{el}\left[AUC\right]\_{0}^{τ}=k\_{el}\left[AUC\right]\_{0}^{\infty }=\frac{FD}{V\_{d}}$ (Α21)

$\frac{A\left(t\right)}{A\left(τ\right)}=1$ (Α22)

*One-compartment model* with two consecutive zero-order, finite-time absorption stages of duration *τ*1 and *τ*2.

For $0<t\leq τ\_{1}$,

$C\left(t\right)=\frac{F\_{1}D}{τ\_{1}V\_{d}k\_{el}}\left(1-e^{-k\_{el}t}\right)$ (Α23)

$\left[AUC\right]\_{0}^{t}=\frac{F\_{1}D}{τ\_{1}V\_{d}k\_{el}}\left[t+\frac{e^{-k\_{el}t}-1}{k\_{el}}\right]$ (Α24)

$C\left(τ\_{1}\right)=\frac{F\_{1}D}{τ\_{1}V\_{d}k\_{el}}\left(1-e^{-k\_{el}τ\_{1}}\right)$ (Α25)

$\left[AUC\right]\_{0}^{τ\_{1}}=\frac{F\_{1}D}{τ\_{1}V\_{d}k\_{el}}\left[τ\_{1}+\frac{e^{-k\_{el}τ\_{1}}-1}{k\_{el}}\right]$ (Α26)

$C\left(t\right)+k\_{el}\left[AUC\right]\_{0}^{t}=\frac{F\_{1}D}{τ\_{1}V\_{d}}t$ (Α27)

$\frac{A\left(t\right)}{A\left(τ\_{1}+τ\_{2}\right)}=\frac{C\left(t\right)+k\_{el}\left[AUC\right]\_{0}^{t}}{C\left(τ\_{1}+τ\_{2}\right)+k\_{el}\left[AUC\right]\_{0}^{τ\_{1}+τ\_{2}}}=\frac{F\_{1}}{F\_{1}+F\_{2}}\frac{t}{τ\_{1}}$ (Α28)

For $τ\_{1}<t\leq τ\_{1}+τ\_{2}$,

$C\left(t\right)=C\left(τ\_{1}\right)e^{-k\_{el}\left(t-τ\_{1}\right)}+\frac{F\_{2}D}{τ\_{2}V\_{d}k\_{el}}\left(1-e^{-k\_{el}\left(t-τ\_{1}\right)}\right)$ (Α29)

$\left[AUC\right]\_{0}^{t}=\left[AUC\right]\_{0}^{τ\_{1}}+C\left(τ\_{1}\right)\frac{1-e^{-k\_{el}\left(t-τ\_{1}\right)}}{k\_{el}}+\frac{F\_{2}D}{τ\_{2}V\_{d}k\_{el}}\left[t-τ\_{1}+\frac{e^{-k\_{el}\left(t-τ\_{1}\right)}-1}{k\_{el}}\right]$ (Α30)

$C\left(t\right)+k\_{el}\left[AUC\right]\_{0}^{t}=\frac{F\_{1}D}{V\_{d}}+\frac{F\_{2}D}{V\_{d}}\frac{t-τ\_{1}}{τ\_{2}}$ (Α31)

$C\left(τ\_{1}+τ\_{2}\right)+k\_{el}\left[AUC\right]\_{0}^{τ\_{1}+τ\_{2}}=\frac{F\_{1}D}{V\_{d}}+\frac{F\_{2}D}{V\_{d}}$ (Α32)

$\frac{A\left(t\right)}{A\left(τ\_{1}+τ\_{2}\right)}=\frac{C\left(t\right)+k\_{el}\left[AUC\right]\_{0}^{t}}{C\left(τ\_{1}+τ\_{2}\right)+k\_{el}\left[AUC\right]\_{0}^{τ\_{1}+τ\_{2}}}=\frac{F\_{1}+F\_{2}\frac{t-τ\_{1}}{τ\_{2}}}{F\_{1}+F\_{2}}$ (Α33)

For $τ\_{1}+τ\_{2}<t$,

$C\left(t\right)=C\left(τ\_{1}+τ\_{2}\right)e^{-k\_{el}\left(t-τ\_{1}-τ\_{2}\right)}$ (Α34)

$\left[AUC\right]\_{0}^{t}=\left[AUC\right]\_{0}^{τ\_{1}+τ\_{2}}+C\left(τ\_{1}+τ\_{2}\right)\frac{1-e^{-k\_{el}\left(t-τ\_{1}-τ\_{2}\right)}}{k\_{el}}$ (Α35)

$\left[AUC\right]\_{0}^{\infty }=\frac{\left(F\_{1}+F\_{2}\right)D}{V\_{d}k\_{el}}=\frac{FD}{V\_{d}k\_{el}}$ (Α36)

$C\left(t\right)+k\_{el}\left[AUC\right]\_{0}^{t}=C\left(τ\_{1}+τ\_{2}\right)+k\_{el}\left[AUC\right]\_{0}^{τ\_{1}+τ\_{2}}=k\_{el}\left[AUC\right]\_{0}^{\infty }=\frac{F\_{1}D}{V\_{d}}+\frac{F\_{2}D}{V\_{d}}$ (Α37)

$\frac{A\left(t\right)}{A\left(τ\_{1}+τ\_{2}\right)}=1$ (Α38)

*Two-compartment model* with zero-order, finite-time absorption of duration *τ,* under the assumption of equal volumes.

For $0<t\leq τ$,

$C\left(t\right)=\frac{FD}{τV\_{c}\left(β-α\right)}\left[\frac{k\_{21}-α}{a}\left(1-e^{-αt}\right)-\frac{k\_{21}-β}{β}\left(1-e^{-βt}\right)\right]$ (Α39)

$C\_{P}\left(t\right)=\frac{FDk\_{12}}{τV\_{c}\left(β-α\right)}\left(\frac{1-e^{-αt}}{α}-\frac{1-e^{-βt}}{β}\right)$ (Α40)

$\left[AUC\right]\_{0}^{t}=\frac{FD}{τV\_{c}\left(β-α\right)}\left[\frac{k\_{21}-α}{a}\left(t-\frac{1-e^{-αt}}{α}\right)-\frac{k\_{21}-β}{β}\left(t-\frac{1-e^{-βt}}{β}\right)\right]$ (Α41)

$C\left(τ\right)=\frac{FD}{τV\_{c}\left(β-α\right)}\left[\frac{k\_{21}-α}{a}\left(1-e^{-ατ}\right)-\frac{k\_{21}-β}{β}\left(1-e^{-βτ}\right)\right]$ (Α42)

$C\_{P}\left(τ\right)=\frac{FDk\_{12}}{τV\_{c}\left(β-α\right)}\left(\frac{1-e^{-ατ}}{α}-\frac{1-e^{-βτ}}{β}\right)$ (Α43)

$\left[AUC\right]\_{0}^{τ}=\frac{FD}{τV\_{c}\left(β-α\right)}\left[\frac{k\_{21}-α}{a}\left(τ-\frac{1-e^{-ατ}}{α}\right)-\frac{k\_{21}-β}{β}\left(τ-\frac{1-e^{-βτ}}{β}\right)\right]$ (Α44)

$\frac{A\left(t\right)}{A\left(τ\right)}=\frac{C\left(t\right)+C\_{P}\left(t\right)+k\_{10}\left[AUC\right]\_{0}^{t}}{C\left(τ\right)+C\_{P}\left(τ\right)+k\_{10}\left[AUC\right]\_{0}^{τ}}=\frac{t}{τ}$ (Α45)

For $τ<t$,

$C\left(t\right)=\frac{FD}{τV\_{c}\left(β-α\right)}\left[\frac{\left(k\_{21}-α\right)\left(1-e^{-ατ}\right)}{a}e^{-α\left(t-τ\right)}-\frac{\left(k\_{21}-β\right)\left(1-e^{-βτ}\right)}{β}e^{-β\left(t-τ\right)}\right]$ (Α46)

$C\_{P}\left(t\right)=\frac{k\_{12}}{β-α}\left(\left(C\left(τ\right)+\frac{k\_{21}C\_{P}\left(τ\right)}{k\_{21}-α}\right)e^{-α\left(t-τ\right)}-\left(C\left(τ\right)+\frac{k\_{21}C\_{P}\left(τ\right)}{k\_{21}-β}\right)e^{-β\left(t-τ\right)}\right)$ (Α47)

$\left[AUC\right]\_{0}^{t}=\frac{FD}{τV\_{c}(β-α)}\left[\frac{k\_{21}-α}{a}\left(τ+\frac{e^{-αt}-e^{-α\left(t-τ\right)}}{α}\right)-\frac{k\_{21}-β}{β}\left(τ+\frac{e^{-βt}-e^{-β\left(t-τ\right)}}{β}\right)\right]$ (Α48)

$\left[AUC\right]\_{0}^{\infty }=\frac{FD}{V\_{c}}$ (Α49)

$\frac{A\left(t\right)}{A\left(τ\right)}=\frac{C\left(t\right)+C\_{P}\left(t\right)+k\_{10}\left[AUC\right]\_{0}^{t}}{C\left(τ\right)+C\_{P}\left(τ\right)+k\_{10}\left[AUC\right]\_{0}^{τ}}=1$ (Α50)

*Two-compartment model* with two consecutive zero-order, finite time absorption stages of duration *τ*1 and *τ*2.

For $0<t\leq τ\_{1}$,

$C\left(t\right)=\frac{F\_{1}D}{τ\_{1}V\_{c}\left(β-α\right)}\left[\frac{k\_{21}-α}{α}\left(1-e^{-αt}\right)-\frac{k\_{21}-β}{β}\left(1-e^{-βt}\right)\right]$ (Α51)

$C\_{P}\left(t\right)=\frac{F\_{1}Dk\_{12}}{τ\_{1}V\_{c}\left(β-α\right)}\left[\frac{1-e^{-αt}}{α}-\frac{1-e^{-βt}}{β}\right]$ (Α52)

$\left[AUC\right]\_{0}^{t}=\frac{FD}{τ\_{1}V\_{c}\left(β-α\right)}\left[\frac{k\_{21}-α}{a}\left(t-\frac{1-e^{-αt}}{α}\right)-\frac{k\_{21}-β}{β}\left(t-\frac{1-e^{-βt}}{β}\right)\right]$ (Α53)

$C\left(τ\_{1}\right)=\frac{FD}{τ\_{1}V\_{c}\left(β-α\right)}\left[\frac{k\_{21}-α}{a}\left(1-e^{-ατ\_{1}}\right)-\frac{k\_{21}-β}{β}\left(1-e^{-βτ\_{1}}\right)\right]$ (Α54)

$C\_{P}\left(τ\_{1}\right)=\frac{FDk\_{12}}{τ\_{1}\left(β-α\right)}\left(\frac{1-e^{-ατ\_{1}}}{α}-\frac{1-e^{-βτ\_{1}}}{β}\right)$ (Α55)

$\left[AUC\right]\_{0}^{τ\_{1}}=\frac{FD}{τ\_{1}V\_{c}\left(β-α\right)}\left[\frac{k\_{21}-α}{a}\left(τ\_{1}-\frac{1-e^{-ατ\_{1}}}{α}\right)-\frac{k\_{21}-β}{β}\left(τ\_{1}-\frac{1-e^{-βτ\_{1}}}{β}\right)\right]$ (Α56)

$\frac{A\left(t\right)}{A\left(τ\_{1}+τ\_{2}\right)}=\frac{C\left(t\right)+C\_{P}\left(t\right)+k\_{10}\left[AUC\right]\_{0}^{t}}{C\left(τ\_{1}+τ\_{2}\right)+C\_{P}\left(τ\_{1}+τ\_{2}\right)+k\_{10}\left[AUC\right]\_{0}^{τ\_{1}+τ\_{2}}}=\frac{F\_{1}}{F\_{1}+F\_{2}}\frac{t}{τ\_{1}}$ (Α57)

For $τ\_{1}<t\leq τ\_{1}+τ\_{2}$,

$C\left(t\right)=\frac{FD}{τ\_{1}V\_{c}\left(β-α\right)}\left[\frac{\left(k\_{21}-α\right)\left(1-e^{-ατ\_{1}}\right)}{a}e^{-α\left(t-τ\_{1}\right)}-\frac{\left(k\_{21}-β\right)\left(1-e^{-βτ\_{1}}\right)}{β}e^{-β\left(t-τ\_{1}\right)}\right]+\frac{F\_{2}D}{τ\_{2}V\_{c}\left(β-α\right)}\left(\frac{k\_{21}-α}{α}\left(1-e^{-α\left(t-τ\_{1}\right)}\right)-\frac{k\_{21}-β}{β}\left(1-e^{-β\left(t-τ\_{1}\right)}\right)\right)$ (Α58)

$C\_{P}\left(t\right)=\frac{FDk\_{12}}{τ\_{1}V\_{c}\left(β-α\right)}\left(\frac{1-e^{-αt}}{α}-\frac{1-e^{-βt}}{β}\right)+\frac{k\_{12}F\_{2}D}{τ\_{2}V\_{c}\left(β-α\right)}\left[\frac{1-e^{-a\left(t-τ\_{1}\right)}}{α}-\frac{1-e^{-β\left(t-τ\_{1}\right)}}{β}\right]$ (Α59)

$\frac{A\left(t\right)}{A\left(τ\_{1}+τ\_{2}\right)}=\frac{C\left(t\right)+k\_{10}\left[AUC\right]\_{0}^{t}}{C\left(τ\_{1}+τ\_{2}\right)+k\_{10}\left[AUC\right]\_{0}^{τ\_{1}+τ\_{2}}}=\frac{F\_{1}+F\_{2}\frac{t-τ\_{1}}{τ\_{2}}}{F\_{1}+F\_{2}}$ (Α60)

For $τ\_{1}+τ\_{2}<t$,

$C\left(t\right)=\frac{\left[C\left(τ\_{1}+τ\_{2}\right)\left(k\_{21}-α\right)+C\_{P}\left(τ\_{1}+τ\_{2}\right)k\_{21}\right]e^{-α\left(t-τ\_{1}-τ\_{2}\right)}}{β-α}+\frac{\left[C\left(τ\_{1}+τ\_{2}\right)\left(k\_{21}-β\right)+C\_{P}\left(τ\_{1}+τ\_{2}\right)k\_{21}\right]e^{-β\left(t-τ\_{1}-τ\_{2}\right)}}{α-β}$ (Α61)

$C\_{P}\left(t\right)=\frac{k\_{12}}{β-α}\left(\left(C\left(τ\_{1}+τ\_{2}\right)+\frac{k\_{21}C\_{P}\left(τ\_{1}+τ\_{2}\right)}{k\_{21}-α}\right)e^{-α\left(t-τ\_{1}-τ\_{2}\right)}-\left(C\left(τ\_{1}+τ\_{2}\right)+\frac{k\_{21}C\_{P}\left(τ\_{1}+τ\_{2}\right)}{k\_{21}-β}\right)e^{-β\left(t-τ\_{1}-τ\_{2}\right)}\right)$ (Α62)

$\frac{A\left(t\right)}{A\left(τ\_{1}+τ\_{2}\right)}=1$ (Α63)

**Table S1**. Effect of selection of rising limb and plateau region for apparent concentration of cyclosporine reference formulation administered orally to fasted subjects. *i* is the index of the point shared by the two straight-line segments, the rising and the horizontal one.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| *I* | *χ*2 | *F.A.T., τ*(h) | *στ*(h) | Slope, a(ng/mL h) | *σa*(ng/mL h) | A∞/*V*d(ng/mL) | *σA∞* (ng/mL) |
| 2 | 1256530 | 6.23 | 0 | 113 | 0 | 702 | 234 |
| 3 | 828832 | 4.25 | 1.57 | 173 | 49 | 729 | 194 |
| 4 | 464242 | 3.09 | 0.87 | 253 | 63 | 755 | 148 |
| 5 | 203957 | 2.70 | 0.43 | 304 | 41 | 777 | 100 |
| 6 | 75516 | 2.70 | 0.25 | 311 | 25 | 792 | 60 |
| 7 | 21998 | 2.78 | 0.14 | 304 | 17 | 801 | 30 |
| 8 | 10486 | 2.87 | 0.09 | 293 | 13 | 805 | 13 |
| 9 | 23905 | 3.06 | 0.12 | 267 | 16 | 805 | 13 |
| 10 | 54703 | 3.30 | 0.17 | 238 | 20 | 804 | 13 |
| 11 | 106136 | 3.60 | 0.24 | 208 | 23 | 803 | 13 |
| 12 | 171630 | 3.95 | 0.31 | 181 | 24 | 804 | 13 |
| 13 | 271530 | 4.44 | 0.42 | 150 | 24 | 806 | 12 |
| 14 | 437032 | 5.32 | 0.67 | 111 | 23 | 808 | 8 |
| 15 | 501448 | 5.87 | 0.77 | 96 | 20 | 810 | 8 |
| 16 | 601990 | 6.72 | 0.97 | 77 | 18 | 811 | 5 |
| 17 | 707491 | 7.77 | 1.25 | 61 | 15 | 812 | 5 |
| 18 | 848129 | 9.49 | 1.80 | 45 | 13 | 811 | 5 |
| 19 | 970339 | 11.66 | 2.55 | 32 | 10 | 810 | 5 |
| 20 | 1062390 | 14.04 | 3.36 | 24 | 8 | 809 | 4 |
| 21 | 1134170 | 16.58 | 4.22 | 19 | 7 | 808 | 3 |
| 22 | 1191740 | 19.22 | 5.09 | 16 | 6 | 807 | 3 |
| 23 | 1238740 | 21.97 | 5.96 | 13 | 5 | 806 | 3 |

**Classical and PBFTPK fits to data**



**Figure S1**. Analysis of paracetamol [13] pharmacokinetic data: Semi-logarithmic fit of falling edge (a) and estimation of absorption termination on apparent absorbed concentration (AAC) data (b); Classical first order absorption and elimination fit (c) and corresponding AAC data analysis (d); PBFTPK analysis using a single, zero-order input, one-compartment model (e) and corresponding AAC data analysis (f). The black triangle denotes the termination of drug absorption. The black dashed lines on the right panels are simulations based on the model used on the left panels. The brown solid lines are the fit for the ascending segment and the red dotted lines are the average level of the plateau values.

 

**Figure S2**. Analysis of ibuprofen [13] pharmacokinetic data. A semi-logarithmic (a, b) and a one-compartment PBFTPK model (c, d) with two zero-order input stages were used. The classical model is not shown because of the very poor quality of the fit. Symbols are explained in Fig. S1.



**Figure S3**. Analysis of almotriptan [13] pharmacokinetic data. Semi-logarithmic (a, b), classical one-compartment model (c, d), and one-compartment PBFTPK model with two zero-order input stages (e, f) are shown. Symbols are explained in Fig. S1.

**     **

**Figure S4**. Analysis of four sets of cyclosporine [13] pharmacokinetic data. Classical two-compartment model (a, b, e, f, i, j, m, n), and two-compartment PBFTPK model with one zero-order input stage (c, d, k, l, o, p) or three zero-order input stages (g, h) are shown. Symbols are explained in Fig. S1.

  

**Figure S5**. Analysis of niraparib pharmacokinetic data [13]. Classical two-compartment model (a, b), and two-compartment PBFTPK model with one zero-order input stage (c, d) are shown. Symbols are explained in Fig. S1.